Remarks

Amendments to the Claims

The amendments to the claims do not add new matter. The amendment to steps (iii) of claims 2 and 3 is supported on page 42, line 18 to page 43, line 9. Recitation of percent homologies in claims 2, 3, and new claims 49-54 is supported on page 12, lines 16-26. New claims 38-48 recite individual members of the Markush groups recited in claims 2 and 3.

Information Disclosure Statement

A copy of the missing document listed on the PTO-1449 Form (the abstract of JP 11318461) accompanies this amendment and is listed on the new PTO-1449 Form that accompanies this response. Please consider the document.

Objection to the Abstract

The Office Action objects to the length of the Abstract. A shorter Abstract accompanies this amendment.

Rejection Under 35 U.S.C. § 101

Claims 2, 3, 29-32, and 35-38 are rejected under 35 U.S.C. § 101 as failing to meet the requirements of a "proper process claim." Applicants respectfully traverse the rejection. The Office Action cites two cases to support the rejection; both are inapt. Both *Ex parte Dunki*, 153 U.S.P.Q. 678 (Bd. App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131 (D.C. 1966) found "use" claims to be improper process claims. "Use" claims recite no steps. Each of

independent claims 2 and 3 explicitly recites three steps. Independent claims 2 and 3 and dependent claims 29-32 and 35-38 are proper process claims. Please withdraw the rejeciton.

Rejection Under 35 U.S.C. § 112 ¶ 2

Claims 2, 3, 29-32, and 35-38 stand rejected under 35 U.S.C. § 112 ¶ 2 as indefinite.[1] Applicants respectfully traverse the rejection.

First, the Office Action asserts it is not clear whether the phrase "in a mammal" applies to all the recited diseases. Claims 2 and 3 are amended to clarify that the phrase "in a mammal" applies to all the recited diseases.

Second, the Office Action asserts the phrases "a first activity" and "a second ativity" are indefinite. The Office Action also asserts the phrase "activity of said [KLK8] polypeptide" is indefinite. Claims 2 and 3 are amended to clarify that the two steps refer to protease activity.

Third, the Office Action contends the third step of each of claims 2 and 3 is indefinite. Claims 2 and 3 are amended to recite "determining an effect of the test compound on a symptom of the disease in an *in vivo* assay."

Fourth, the Office Action contends it is unclear in claim 3 whether the phrase "a KLK8 polypeptide" refers to one or more different polypeptides. Claim 3 is amended to clarify that the KLK8 polypeptide of step (ii) is the KLK8 polypeptide of step (i).

Fifth, the Office Action asserts that the phrase "known regulator" in claim 3 is indefinite. Claim 3 is amended to delete the word "known."

Finally, claims 2, 30-32, and 36-38 are amended to correct antecedent basis as the Office Action suggests.

[1] The Office Action refers to claims 3 and 4, but the text of the rejection refers to claims 2 and 3.

Please withdraw the rejection.

Rejection Under 35 U.S.C. § 112 ¶ 1 (enablement)

Claims 3, 29-32, and 35-38 are rejected under 35 U.S.C. § 112 ¶ 1 as not enabled for their full scope. Applicants respectfully traverse the rejection.

The legal test for whether a disclosure provides adequate enablement for a generic claim is that "the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art." *In re Fisher*, 427 F.2d 833, 839, 166 U.S.P.Q. 18, 24 (C.C.P.A. 1970). Claims 3, 29-32, and 35-38 meet this standard.

As an initial matter, a large portion of the rejection is based on the breadth of the genus of KLK8 polypeptides recited in claim 3. To advance prosecution, claim 3 is amended to recite a genus of KLK8 polypeptides which "comprise an amino acid sequence which has at least 90% homology with the amino acid sequence SEQ ID NO:2." This amendment moots that portion of the rejection.

The Office Action also contends that knowledge of the specific steps and reagents to be used are required to enable identification of modulators of KLK8 activity. Assays for KLK8 activity are known in the art as disclosed in Example 9 on pages 113-114 of the specification.

Finally, the Office Action faults the specification for not providing evidence that KLK8 causes or cures any specific disease. This is a red herring, because this information is not required to enable the claimed screening methods. None of the methods recites or requires treatment or cure of a specific disease. KLK8 need not be the cause of a disease to be a useful target for treating a symptom of a disease.

The Office Action has not made a *prima facie* case that claims 3, 29-32, and 35-38 are not enabled. Please withdraw the rejection.

Rejection Under 35 U.S.C. § 112 ¶ 1 (written description)

On page 10 the Office Action rejects claims 3, 29-32, and 35-38 under 35 U.S.C. § 112 ¶ 1 as insufficiently described because the specification allegedly does not teach methods of "identifying modulators of human KLK8 or variants thereof and then testing said modulators in vivo." Applicants respectfully traverse the rejection.

The purpose of the written description requirement is to ensure that the specification conveys to those skilled in the art that the applicants possessed the claimed subject matter as of the filing date sought. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 U.S.P.Q.2d 1111, 1117 (Fed. Cir. 1991). The present specification meets this standard. First, independent claim 3 as amended recites a genus of KLK8 polypeptides which "comprise an amino acid sequence which has at least 90% homology with the amino acid sequence SEQ ID NO:2." As acknowledged in Example 11 of the PTO's Written Description Training Materials, once an amino acid sequence (here, SEQ ID NO:2) is disclosed to one of skill in the art, she can envision even amino acid sequences 85% identical to the disclosed amino acid sequence.

Second, a specification need not teach, and preferably omits, what is well known in the art. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986). The specification describes methods of identifying modulators of protease activity of human KLK8 polypeptides. See Example 9 on pages 113-114. The specification also discloses determining effects of test compounds on a symptom of diseases in *in vivo* assays. See page 42, line 18 to page 43, line 9. *In vivo* model systems for the recited disorders were well known in the art at the

August 30, 2003 priority date of this application. *See, e.g.*, Dittmar,[2] McGowan,[3] Ward,[4] and El-Sabban[5] (cardiovascular diseases); Sigurdson,[6] Keene,[7] (neurological disorders); Fuentealba & Aburto,[8] Anand,[9] and Velasquez,[10] (metabolic diseases); Lein,[11] Sezen,[12] and O'Neill[13] (urological diseases); and Jakimiuk,[14] Wang,[15] and Kamtchoing[16] (reproductive disorders).

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[2] Dittmar *et al.*, "External Carotid Artery Territory Ischemia Impairs Outcome in the Endovascular Filament Model of Middle Cerebral Artery Occlusion in Rats," Stroke 34, 2252-57, July 31, 2003, provided with the accompanying IDS.

[3] McGowan *et al.*, "Unloading-induced remodeling in the normal and hypertrophic left ventricle," Am. J. Physiol. Heart Circ. Physiol. 284, 2061-68, February 6, 2003, provided with the accompanying IDS.

[4] Ward *et al.*, "Reduced contraction strength with increased intracellular [Ca2+] in left ventricular trabeculae from failing rat hearts," J. Physiol. 546.2, 537-50, 2003, provided with the accompanying IDS.

[5] El Sabban *et al.*, "Angiotensin II binding and extracellular matrix remodelling in a rat modelof myocardial infarction," J. Renin Angiotensin Aldosterone Syst. 1, 369-78, 2000, provided with the accompanying IDS.

[6] Sigurdson *et al.*, "Immunization with a Nontoxic/Nonfibrillar Amyloid-b Homologous Peptide Reduces Alzheimer's Disease-Associated Pathology in Transgenic Mice," Am. J. Pathol. 159, 539-47, August 2001, provided with the accompanying IDS.

[7] Keene *et al.*, "Tauroursodeoxycholic acid, a bile acid, is neuroprotective in a transgenic animal model of Huntington's disease," Proc. Natl. Acad. Sci. USA 99, 10671-76, August 6, 2002, provided with the accompanying IDS.

[8] Fuentealba & Aburto, "Animal models of copper-associated liver disease," Comparative Hepatology 2:5, 12 pages, April 3, 2003, provided with the accompanying IDS.

[9] Anand *et al.*, "Endothelin is an important determinant of renal function in a rat model of acute liver and renal failure," Gut 50, 111-17, 2002, provided with the accompanying IDS.

[10] Velasquez *et al.*, "Leptin and Its Relation to Obesity and Insulin in the SHR/N-corpulent Rat, A Model of Type II Diabetes Mellitus," Int. Jnl. Experimental Diab. Res. 2, 217-23, 2001, provided with the accompanying IDS.

[11] Lein *et al.*, "The pharmacological effect of the gonadotrophin-releasing hormone on experimental cryptorchidism in rats," Scand. J. Urol. Nephrol. 30, 185-91, 1996 (abstract), provided with the accompanying IDS.

[12] Sezen *et al.*, "FK506 binding protein 12 is expressed in rat penile innervation and upregulated after cavernous nerve injury," Int. J. Impot. Res. 14, 506-12, December 2002 (abstract), provided with the accompanying IDS.

[13] O'Neill *et al.*, "Pharmacological properties of A-204176, a novel and selective alpha1A adrenergic agonist, in in vitro and in vivo models of urethral function," Life Sci. 70, 181-97, November 30, 2001 (abstract), provided with the accompanying IDS.

[14] Jakimiuk *et al.*, "Aromatase mRNA expression in individual follicles from polycystic ovaries," Mol. Human Reproduction 4, 1-8, 1998, provided with the accompanying IDS.

One skilled in the art at the priority date of this application would understand that Applicants possessed the claimed subject matter. Please withdraw the rejection.

Rejection Under 35 U.S.C. § 103(a)

The Office Action rejects claims 2, 3, 29, and 35 under 35 U.S.C. § 103(a) as *prima facie* obvious over Sampaio[17] in view of Yoshida,[18] Colman,[19] and Shimizu.[20] Piesecki[21] is added to the this combination to reject claims 30, 31, 36, and 37 as *prima facie* obvious. Applicants respectfully traverse the rejection.

The U.S. Patent and Trademark Office bears the initial burden of establishing a *prima facie* case of obviousness. The *prima facie* case requires three elements:

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

M.P.E.P., 8th ed., § 2142. To advance prosecution, claims 2 and 3 are amended to delete gastroenterological disorders. None of the cited references teaches or suggests a connection

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[15] Wang *et al.*, "Reproductive Aging in the Male Brown-Norway Rat: A Model for the Human," Endocrinology 6, 2773-81, 1993, provided with the accompanying IDS.

[16] Kamtchoing *et al.*, "Age-Related Changes in the Function of the Pituitary-Gonadal Axis in a Sterile Male Rat Mutant (hd/hd)," Biology of Reproduction 45, 11-19, 1991, provided with the accompanying IDS.

[17] Sampaio *et al.*, *Immunopharmacology 32*, 62-66, May 1996.

[18] Yoshida *et al.*, *Gene 213*, 9-16, June 1998.

[19] Colman *et al.*, *Immunopharmacology 43*, 103-08, September 1999.

[20] Shimizu *et al.*, *J. Biol. Chem. 273*, 11189-96, May 1998.

[21] Piesecki *et al.*, *Biotech. Bioeng. 42*, 187-84, June 1993.

between KLK8 and disorders recited in amended claims 2 and 3; thus, claims 2 and 3 and dependent claims 29-31, 36, and 37 are not *prima facie* obvious over the cited references.

Please withdraw the rejection.

Respectfully submitted,

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/Lisa M. Hemmendinger/

Date: October 8, 2008 By: _____

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